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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/355,210	07/12/2000	Raffaello Giorgi	515-4167	6135

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EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/17/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/355,210	Giorgi
Examiner	**Art Unit**
David Lukton	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 17, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-9, and 11-18* is/are pending in the application.

4a) Of the above, claim(s) *4* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, 5-9, and 11-18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 20 (filed 10/17/02), claims 1, 3, 5, 9, 12-14 have been amended, and claims 2 and 10 cancelled. Claims 1, 3-9, 11-18 are pending. Claim 4 remains withdrawn from consideration; claims 1, 3, 5-9, 11-18 are examined in this Office action.

Applicants' arguments filed 10/17/02 have been considered and found persuasive in part. The previously imposed prior art rejections are withdrawn.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-9 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have asserted (p. 27) that they have subjected "the compounds of the invention" to *in vitro* assays, as described on page 27 (and references cited therein). Applicants have also asserted that "the compounds of the invention" were "active" in the assays. These assertions are left unchallenged at this time. In the cited claims it is

asserted that the compounds are effective to treat various diseases. However, there is no evidence that this is the case. Merely because the asserted antagonism may take place *in vivo* does not mean that there exists a single disease or disorder for which benefit will accrue to a patient. The degree of antagonism might not be sufficient to achieve a perceptable effect; moreover, the NK-2 receptor might not be a critical element in any of the recited disorders, i.e., even if the NK-2 receptor could be blocked to the extent of 100% *in vivo*, it does not necessarily mean that the symptoms of any disease will recede. The fact is that, whether has shown antagonism of a receptor or stimulation of the same, extrapolation from this to treatment of diseases leads to "unpredictable" results. As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

In response to the foregoing, applicants have argued that the mere assertion by an applicant that a given dosage of a compound is effective to treat a given disease is effective to enable one to treat the disease so recited. However, applicants are not correct. One could assert, for example, that taking a single 500 mg vitamin C tablet is

effective to treat AIDS, Alzheimers disease, and cancer. However, the fact that this has now been asserted does not mean that vitamin C will be effective in this regard. Next applicants have argued that, during the course of development of a drug that ultimately proves to be effective in humans, pharmaceutical company researchers routinely undertake experiments determine whether or not *in vivo* efficacy in animals can be demonstrated. This particular point is correct. But applicants then go on to imply that if someone tests a compound on an animal to determine if it is efficacious, the mere act of administering the compound to the animal means that the compound will be therapeutically effective in humans, irrespective if it shows any activity in the animal subject. However, this is not true. The reality in pharmaceutical research is that only a small number of the compounds which are effective in *in vitro* assays prove to be effective in animals; of the compounds which are effective in animals, only a small handful are effective in humans.

Next, applicants have argued that the "therapeutic utility statement" should not be confused with FDA requirements. However, at no point has the examiner suggested that applicants must meet FDA requirements.

Next, applicants have argued that the examiner has imposed a utility rejection. However, at no point in the prosecution has a rejection under 35 USC §101 been imposed. For clarification, a rejection under 35 USC §101 is not now being imposed.

Thus, the question of whether a rejection under 35 USC §101 would be proper or improper need not be discussed further.

In the previous Office action, the following references and accompanying teachings were cited by the examiner:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH_2 (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) 55 (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4-D-Phe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

In response to the foregoing, applicants have argued that success in the pharmaceutical industry is inevitable, as long as some *in vitro* activity can be demonstrated. It may be true that if a compound has survived the multi-year research hurdles, and the tens of millions of dollars necessary to discover the compound and its *in vivo* activities, then, at that point it might require only routine experimentation to demonstrate that which has already been determined to be true. In other words, if one starts with 10,000 compounds which demonstrate suitable *in vitro* activity, and invests 10 years and millions of dollars to discover one compound out of the 10,000 which are therapeutically effective, at that point, it would only require routine experimentation for someone else to confirm what has already been determined to be true. The teachings of the foregoing references (Torsello, McFadyen, Keith, Xiao and Lunec) are consistent with the examiner's position that one cannot predict therapeutic efficacy on the basis of in vitro activity. If applicants arguments with respect to routine experimentation were correct,

then such absence of correlation between *in vitro* activity and *in vivo* activity would not have been observed. Applicants have also argued that the specific therapeutic objectives of the authors of the cited references (Torsello, McFadyen, Keith, Xiao and Lunec) were not identical to those which are the subject of the rejected claims. While this may be true, the extrapolation is, in broad sense, the same. In a broad sense, the first question is, can one predict the physiological activity of a compound based upon its ability to antagonize or stimulate a given receptor? And second, if such physiological activity could be predicted, can one then predict the physiological effects of the compound when administered to an ill patient? As it happens, the answer to the first question is in the negative. Even in normal healthy persons, receptor antagonistic or agonistic acitivity is not predictive of physiological activity in the intact mammal (or human). And if one cannot predict physiological activity in healthy animals, one can have no hope of predicting therapeutic efficacy in an animal whose normal homeostatic mechanisms have been severely disturbed.

Applicants have also pointed to the following references:

Evangelista, S. (*Current Pharmaceutical Design* **7**(1) 19-30, 2001)

Holzer, Peter (*Current Opinion in Pharmacology* **1**(6) 583-590, 2001)

Rogers, Duncan F. (*Expert Opinion on Therapeutic Patents* **11**(7), 1097-1121, 2001)

No doubt there is some speculation in the literature that neurokinins play some peripheral role in the etiology or manifestations of the diseases that are recited in claim 18. Perhaps also, there have been a few successes in animal models of asthma. But for most of the diseases that are recited in claim 18, it is fair to assume, based on the record thus far, that all attempts at treating the diseases of claim 18 have met with failure, or else that no one has attempted to treat the recited disorders using neurokinin receptor antagonists. For example, in which reference are results presented which demonstrate efficacy in the treament of kidney infections? Are there even assertions in the non-patent literature that bacterial growth can be inhibited by neurokinin receptor antagonists? As indicated, it may be the case that there have been a few successes in animal models of asthma. But as it happens in this, as well as all other areas of pharmacology, structure/activity relationships are unpredictable. It has not been determined what degree of antagonism is sufficient to achieve a perceptable effect; moreover, the NK-2 receptor might not be a critical element in any of the recited disorders, i.e., even if the NK-2 receptor could be blocked to the extent of 100% *in vivo*, it does not necessarily mean that the symptoms of any disease will recede. Then there are issues of bioavailability and pharmacokinetics. Thus, one cannot merely point to the success of another scientist in the treatment of asthma using a neurokinin receptor antagonist and argue that <u>all</u> neurokinin receptor antagonists will be therapeutically

Consider also the following references:

- Foster, P. S. (*Clinical and Experimental Allergy* **29** (1) 12-6, 1999) discloses (page 13, col 1) that anti-IL-4 mAb's are effective in attenuating airway hyperresponsiveness if administered during the primary sensitization phase, but not during the period or direct provocation of the airways with allergen. This raises the issue of the timing of administration of the potentially "active agent", and raises the possibility that, even if the claimed compounds are effective to inhibit bronchoconstriction if administered before allergen challenge, they might not be effective if administered after symptoms of bronchoconstriction had already developed. The claims encompass both possibilities.

- Henderson (*J. Immunol.* **164**, 1086-95, 2000) discloses that administration of soluble IL-4 receptor (sIL-4R) prior to OVA challenge inhibited the inflammatory response, but only if administered intranasally. If administered i.p., the sIL-4R was not effective. This raises the possibility that even if the claimed compounds are effective to inhibit bronchoconstriction if administered directly to the lung, they might not be effective if adminstered orally. The claims encompass both possibilities.

- Wallace J. L. (*Regulatory Peptides* **73** (2) 95-101, 1998) discloses a compound that is, on the one hand an antagonist of neurokinin receptors, but on the other hand, was not effective to treat colitis.

- Fahy J. V. (*American Journal of Respiratory and Critical Care Medicine* **152** (3) 879-84, 1995) discloses that a neurokinin receptor antagonist was not effective to treat asthma.

- Evangelista S. (*Neuropeptides* **30** (5) 425-8, 1996) discloses that a neurokinin receptor antagonist was not effective to treat colitis.

- Reinshagen M. (*Journal of Pharmacology and Experimental Therapeutics* **286**(2) 657-61, 1998) discloses that a neurokinin receptor antagonist was not effective to treat colitis.

- Girard V (*European Respiratory Journal* 8 (7) 1110-4, 1995) discloses that SR 140333 is a neurokinin receptor antagonist which is not effective as an antitussive.

- Biyah K (*European Journal of Pharmacology* 308 (3), 325-8, 1996) discloses a neurokinin receptor antagonist which is not effective to treat asthma.

Accordingly, merely because NK-2 receptors can be antagonized *in vitro* does not mean that any of the compounds will be useful to treat asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, spasms of the bladder, spasms of the ureter, kidney infections, or colics. It follows that "undue experimentation" would be required to practice the invention of claims 8, 9 and 14.

The following is suggested:

> *A method of inhibiting bronchoconstriction comprising administering a compound according to claim 1 to a mammal in need thereof for a time and under conditions effective to antagonize NK-2 (neurokinin-2) receptors.*

*

Claims 1, 3, 5-9, 11-18 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 1, within the last 14 lines, there are a total of five left-handed parentheses, and only <u>two</u> right-handed parentheses. There should be an equal number of each.

- The following is recited four lines from the end of claim 1:

"as R^{12} or a group 4-nitrobenzyl.

Here, a period follows "nitrobenzyl". This period should be eliminated and replaced with a comma or semicolon.

- In claim 5, the term "general" is superfluous and can be eliminated.
- Claim 3 is dependent on a cancelled claim.
- In claim 3, compound "aq" contains the term "chinyl". If this term is going to be used, it should be defined somewhere in claim 3.
- In claim 3, there are at least four compounds ("at" "an" "ap", "au") in which the term "glycopiranos-1-yl" is used. This should instead be spelled with a "y" instead of an "i", i.e., the following: glycopyranos-1-yl
- In claim 3, there is a period following the name of compound "am". This period should be eliminated.

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. §102(b) as being anticipated by Kyoko JP 06172385.

Kyoko discloses the compound of formula II in col 1, lines 15-20

R1 = side chain of tryptophan;

R2 = side chain of tryptophan;

R3 = isopropyl

R4 = $-CH_2-OH$

Thus, the claim is anticipated.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800